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Schizophrenia's Relationship with Cardiovascular Morbidity and Mortality

Hannah Jorgensen
Augsburg University

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Hannah Jorgensen, MA, PA-S2

Advisor: Professor Vanessa Bester, PA-C

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Abstract

Premature morbidity and mortality due to cardiovascular disease (CVD) disproportionately affects individuals with schizophrenia. This research paper systematically reviews articles that examine the theories and causes of increased CVD risk in individuals with schizophrenia. The findings of the review indicate that there are biological, environmental and sociocultural components of the relationship between schizophrenia and cardiovascular disease. Inflammation from the progression of chronic schizophrenia appears to play a part. The side-effect profile of the medications used to treat schizophrenia cause CVD risk factors. The secondary and tertiary symptoms of the disease process result in problems in motivation, cognitive function and self-isolation, all which contribute to CVD risk. Sociocultural factors such as increased poverty, homelessness and food insecurity are also higher in this population, which are associated with increased cardiovascular morbidity. In conclusion, further research into contributing factors and funding for services is needed to better understand this issue and reduce the associated public health disparities.

Introduction

Individuals with schizophrenia are dying earlier as compared to the general population[1, 2]. People with severe mental illness (including schizophrenia, major depression and bipolar disorder) are dying 10-25 years earlier and those with schizophrenia proper have a 2 to 2.5 times higher mortality rate.[1] This profound discrepancy can be primarily attributed to cardiovascular disease[1-4]. Cardiovascular disease (CVD) is a broad term that encompasses many disease processes including but not limited to: coronary heart disease, atherosclerosis, hypertension, peripheral artery disease, cerebrovascular disease and stroke. CVD has many risk factors and sequelae. The most pertinent risk factors in the schizophrenia population are diabetes mellitus (two to three times higher in individuals with schizophrenia[1, 5]), cigarette smoking, poor diet and physical inactivity. Another important risk factor is metabolic syndrome, characterized by hypertension, hyperlipidemia, high blood glucose and centralized obesity[5].

Background on Schizophrenia and Cardiovascular Disease

Schizophrenia is defined by the National Institute of Mental Health as a "chronic and severe mental disorder that affects how a person thinks, feels and behaves[6]." It is also characterized by a loss of touch with reality and a chronic disability in day-to-day functioning. In the DSM-V, the official diagnostic manual for mental health disorders[7], schizophrenia is defined by the presence of both "positive" and "negative" symptoms. Positive symptoms indicate the presence of symptoms that were not previously there, such as delusions, hallucinations or disorganized thoughts and behaviors. Negative symptoms include flat affect, anhedonia (lack of pleasure in daily activities), amotivation and poverty of speech[7]. Negative symptoms can present functionally as poor hygiene, lack of social skills and an inability to stay motivated or be a part of "normal" activities such as work, school or home life[6].

Cardiovascular disease (CVD) risk can be qualified through patient report. This is via previously discussed risk factors such as cigarette smoking, metabolic syndrome and lack of physical activity. One measure of quantifying cardiovascular risk is the ASCVD 10-year or lifetime risk scale adopted by the American Heart Association[8]. This scale is widely accepted in the medical community as a way to quantify CVD risk, outcomes and choose appropriate treatment options. The ASCVD looks at patient variables of lipid levels (LDL and HDL), cigarette smoking, age, blood pressure and gender to measure cardiovascular risk[8]. There are alternative tools to use that take into account the patient's ethnicity and racial background. Diabetes mellitus (DM2) is also well established as a CVD risk factor. DM2 can be quantified in various ways, but in the literature most often the measurements used are HbA1C or C-peptide markers via serum laboratory draws[5].

Impact of Problem

The evidence of premature mortality and significant morbidity from cardiovascular disease in people with schizophrenia is remarkable. A large-scale meta-analysis completed in 2017 by Correll et. al[2] found that 10% of individuals with severe mental illness have CVD by age 50. By having a severe mental illness the lifetime risk of having CVD increases by 53% and there is an 85% increased risk of CVD mortality.

There is an additional financial burden associated with the high incidence of cardiometabolic comorbidities in the schizophrenia population. This is attributed to increased inpatient hospital readmissions (within 30 days) and resulting increased monetary spending by taxpayers[9]. All of this highlights the glaring public health disparity and crisis with which the medical community is currently faced.

The increased incidence of morbidity and mortality from cardiovascular disease in individuals with schizophrenia is profound. This is both a public health crisis and an economic problem and is a concern that the medical community needs to address. There are initiatives and guidelines that are beginning to address these problems[20], but the stigma and tertiary symptoms of schizophrenia are still barriers to prioritization of these issues within the medical community[1]. Continued research and education is key to ensure that this vulnerable population does not continue to slip through the cracks of our medical system.

Literature Review

The question is then raised—why do individuals with schizophrenia have a higher rate of cardiovascular disease (CVD) and premature mortality? The answer is complex and dynamic, with many contributing factors. The anti-psychotic medications used to treat schizophrenia play a significant part due to their side effects, which cause weight gain, metabolic symptoms and diabetes mellitus[10]. The negative symptoms of schizophrenia itself can contribute as they affect a person's motivation, cognition and functional ability to cook healthy meals and participate in regular physical activity[1,24,25]. Severe mental illness is often linked to low socioeconomic status[1], which is not often studied in terms of its impact on these individual's cardiovascular health. It is shown that low SES is linked to food deserts, poor diet and physical inactivity that cause an increased disparity in CVD risk factors[1,24]. Individuals with low SES and schizophrenia both have a higher incidence of cigarette smoking[6,24] compared to their more socioeconomically affluent counterparts, another risk factor for developing CVD[6]. Lack of access to care and provider judgment can also play a part[1, 11]. Another developing theory for the significantly high

comorbidity is the inflammatory theory of schizophrenia, which postulates a possible biological or genetic link between the two disease processes[12-14].

Anti-Psychotic Medications and Cardiovascular Disease

Anti-psychotic medications are first-line treatment for schizophrenia[6]. These include first-generation medications such as Haldol, Thorazine and Clozapine, which are now generally reserved for refractory cases of schizophrenia due to possible irreversible neurological side effects. The more commonly used medications are second-generation atypical antipsychotics (such as Depakote, Seroquel and Risperdal). These atypical anti-psychotic medications, while much safer in terms of neurological side effects, can cause significant weight gain and obesity and have resulting diabetes mellitus and metabolic syndrome[5, 6, 10, 15].

Studies are being done to try and extrapolate the incidence of metabolic syndrome (as a CVD risk factor) in patients with schizophrenia from anti-psychotic use. Cordes et. al[15] completed a study comparing anti-psychotic naïve men and women with schizophrenia to healthy control participants. They found increased incidence of metabolic syndrome (specifically increased blood pressure, waist circumference and blood glucose) in people with schizophrenia; although the findings were not significant enough to show that anti-psychotic naïve patients have an increased risk of developing metabolic syndrome. The researchers did cite gaps in their data and that further research may show that anti-psychotic naïve patients do have an increased risk of developing metabolic syndrome independent of medication use.

In contrast, Catts and O'Toole[16] decisively state that anti-psychotics do not significantly contribute to CVD morbidity and mortality in schizophrenic individuals. They report that instead long-term maintenance with anti-psychotic medications, particularly a bi-monthly injection medication such as Risperdal Consta, reduces symptoms and remissions and therefore manages

comorbidities. The authors propose that CVD risk, morbidity and mortality are primarily associated with prolonged periods of psychosis without remission. These prolonged periods of psychosis lead to both negative symptoms and a lack of insight and therefore poor preventative care and the associated symptoms of schizophrenia. The caveat to this opposing point of view is that the authors of the article receive funding from Lilly, Janssen and other large pharmaceutical companies that produce atypical anti-psychotic medications.

Inflammatory Theory of Schizophrenia

The role of inflammation in disease processes and pathology has permeated recent medical research. The effects of inflammatory processes are being investigated in relation to all systems of the body. Research is now well established linking metabolic syndrome and cardiovascular disease to inflammatory processes. There are various theories regarding the mechanisms of this process and it is being continuously refined and studied. One theory poses that there is a link with adipocytokines from the gut and resulting inflammatory processes, and metabolic syndrome (and it's sequelae of CVD)[17]. This specific theory highlights the complex interaction of hereditary, biological and environmental etiologies of metabolic syndrome and cardiovascular disease.

Research is now investigating schizophrenia as a function of inflammation and inflammatory processes[12-14]. This theory revolutionized the study of the biological and physiological origins of severe mental illnesses, as previously the focus was on neurobiological and neurochemical processes. The core of the research is looking at cytokines and various inflammatory markers (such as alpha-TNF) and their concentrations in people affected by severe mental illness (schizophrenia, in this case). The prevailing premise is that the inflammatory processes that then happen in the brain could have neuropsychological sequelae. Studies show

mixed findings as this research is new and still being understood. This research again highlights the complex etiology and pathophysiology of schizophrenia and the contributions from both environment and genetics.

Balostev et. al[14] used a case-control design to investigate the relationship between changes in specific inflammatory markers in individuals with schizophrenia with comorbidities of CVD and/or diabetes mellitus. Their findings were mixed, but increased pro-inflammatory markers, including cytokines and growth factors (IL-2 and ILF-y specifically), were present in individuals with chronic schizophrenia. While the research showed that the progression of chronic schizophrenia was significantly linked to inflammation, the findings were vague when attempting to assign significance to a relationship with CVD presentations. A key significant finding of the study was that individuals with schizophrenia who had CVD (as measured by a hyperlipidemia risk factor) showed signs of chronic pro/anti-inflammatory imbalance via their inflammatory disease-markers (cytokines and growth factors). A point of note is that for some statistical analyses the researchers set their p-value to < 0.1 as opposed to the generally accepted $p < 0.05$ as the lower value "failed to identify important variables for the final model.[14]"

These inflammatory processes could also have implications in the link between schizophrenia and metabolic syndromes. Gut microbes and mircroflora and resulting inflammation and disease processes (such as celiac disease) is a well-studied process in the academia of gastrointestinal and dietary sciences. Joseph et. al[13] looked at inflammatory markers in the gut to discern if there were any significant changes in gut microbes and resulting immune dysfunction in people with schizophrenia. Specifically they looked at short chain fatty acids, which are metabolites of dietary fiber by gut microbes. Short chain fatty acids are metabolized by both immune and metabolic pathways, making them ideal for theoretical research comparing

neurobiological (schizophrenia) and metabolic disease processes. The findings were preliminary and there were no statistically significant causational findings noted. The researchers did state that there was some evidence of increased gut inflammatory markers in people with schizophrenia, which would indicate a link to immune dysfunction and possible poor neuropsychological outcomes.

Sociocultural Influence on CVD risk factors

Socioeconomic (SES) and racial disparities affect outcomes in schizophrenia[1,6,24]. Mangurian et al.[18] found that diabetes mellitus was more prevalent in adults with severe mental illness than in the general population, a finding echoed by other studies[2, 5]. Their data also indicated that non-White adults with severe mental illness were at a two to three times increased risk of developing diabetes mellitus as compared to White adults.

Chronic schizophrenia is associated with poverty, unemployment, homelessness and social isolation[1, 25, 27]. These states put individuals at risk for food insecurity and unhealthy diets, lack of health insurance, lack of access to healthcare and a general poor quality of life, all leading to an increased CVD risk[1,24]. Individuals with chronic schizophrenia often end up unemployed[25], and in the United States this would result in utilizing Social Security Income (income that is below the poverty limit) for financial support. Due to chronic disabling symptoms, they are also often estranged from family[25] and many are living in homeless shelters or institutions. All of these factors cause people with schizophrenia to rely on food stamps and food shelves for the context of their diet, often resulting in highly-processed, high-fat and carbohydrates and low in fresh fruits and vegetables[28]. This also results in food insecurity, where individuals do not always have stable access to nutritious food. Additionally, there is a high incidence of homelessness within this population, which limits an ability to store food or

make healthy meals[27]. Healthcare access is limited by insurance, transportation and ability to pay co-pays, which also has trickle-down effects on CVD health and risk factors.

Provider attitudes can be a barrier to quality care. The World Health Care Organziation[1] indicates that one of the primary reasons for negative provider attitudes is due to stigma. General medical providers often have little understanding or knowledge about psychosis and schizophrenia. This leads to misunderstanding, judgment and mistrust on both sides of the provider-patient relationship. Schizophrenia is a disorder already defined by paranoia and altered thinking[7], and this mistrust or misconstrued relationship can lead to a lack of engagement or a complete disengagement from medical care. This is problematic as preventative care is key in both promoting a heart healthy lifestyle and screening and early treatment of cardiovascular risk factors.

The symptoms and progression of schizophrenia itself also play a part in increasing CVD risk factors[1]. Negative symptoms of schizophrenia cause poor hygiene, social isolation and a lack of motivation[6,7,28]. This can make it difficult for a person to exercise regularly, cook, prepare healthy meals and follow-up with medical care[26,28] (often fraught with complex labs, appointments and instructions)[19]. Additionally social isolation is independently associated with increased symptoms of inflammation, food insecurity and poor nutrition—all linked to CVD risk factors[28]. Schizophrenia is also associated with increased substance abuse, including cigarette smoking[2]. Cigarette smoking is considered a CVD risk factor per the ASCVD 10 year risk guidelines[8].

Interventions for reducing cardiovascular risk factors

The chronic and pervasive nature of cardiovascular morbidity and mortality in individuals with schizophrenia is clear. So what can we, as a medical community, do to address this issue?

Public health awareness around this topic is increasing. Healthy People 2020 initiatives through the Office of Disease Prevention and Health Promotion[20] are specifically indicating a need for primary care clinics to integrate mental health services on site. These public health initiatives will ideally be implemented across the nation by the year 2020 and their focus on integration of services emphasizes increased awareness.

Exercise-specific Interventions

Increased physical activity is a healthy lifestyle factor that can reduce cardiovascular risk[8]. Naslund et. al[21] studied increased physical activity in people with severe mental illness as a function of utilizing "wearable devices" (such as a Fit Bit). The study participants wore the devices daily, were given recommendations to complete 150 minutes of moderate exercise per week, intake a healthy diet and received personal support services through the study. The findings were mixed on whether or not the "wearable devices" themselves increased fitness (although the participants did lose weight during the study). The researchers indicated that adherence, health literacy and cost were all barriers in generalizing use of the devices outside of their study parameters.

Other research indicates that in people with schizophrenia the most influential factor in increasing physical activity is with a health professional's specific encourgament[19]. The research by Twyford and Lushford[19] indicated that any encouragement or mention regarding physical activity by a health professional, no matter the context, was at least mildly effective. This is a key point for primary care and medical providers as it is an easy intervention to implement at any preventative appointment.

Diet-specific interventions

Regular consumption of a heart-healthy diet will reduce cardiovascular risk[8]. The Mediterranean Diet could have an increased potential to reduce CVD risk in people with schizophrenia as it may target specific gut metabolites and inflammatory processes[13]. These findings were statistically insignificant however, and the researchers cautioned that further research needed to be done before definitively saying that the Mediterranean Diet is the best diet for reducing CVD risk in schizophrenia. Evidence still exists that it is an effective heart-healthy diet, although one of many options (such as the DASH diet, or general reduction of dietary saturated fat)[23].

Provider-specific Interventions

Healthcare providers are often unfamiliar or uncomfortable with schizophrenia and healthcare clinics do not have mental healthcare integrated on site[1, 20]. Researchers polled primary care providers on whose role it was to follow up on metabolic monitoring of individuals taking anti-psychotic medications: the patient's primary care provider or their psychiatrist [11]. The researchers received three different responses from the providers: 1) primary care provider's role to prescribe the medications and monitor 2) psychiatrist's role to do both 3) psychiatrist should prescribe and the primary care should do the metabolic monitoring. In this case, it is likely that some patients psychiatric and/or CVD care was falling through the cracks, which could easily contribute to increased morbidity and mortality. These findings indicate that coordination of care between medical and mental health providers is crucial.

A Cochrane Review[22] analyzed the effectiveness of offering general physical advice to people with severe mental illness. They found that offering only general advice as a medical provider was a statistically ineffective intervention at improving patient outcomes and quality of life. This shows the need for focused, specific interventions when it comes to reducing CVD risk in individuals with schizophrenia.

Methods

Pub Med database through the Augsburg Lindell Library was searched for any articles containing the keywords "schizophrenia," "serious mental illness," "cardiovascular disease," and "metabolic syndrome". The researcher initially reviewed 47 articles, which needed to include information on both schizophrenia and cardiovascular disease. Thirty-five of those articles were moved into RefWorks database for further review. The articles were then narrowed down via abstract and availability (two articles were not available via inter-library loan) as they pertained to the research question. Articles that looked only at non-CVD risk factors (such as fatty liver or diabetes mellitus), genetic markers or specific populations (such as the elderly, racial groups or long-term inpatient patients) were discarded. Initially sixteen peer-reviewed articles were included in the review. As the researcher reviewed the articles and supplemental information was needed six articles were added. Twenty-two peer-reviewed articles, one response to a peer-reviewed article and five supportive sources were chosen to be included in this review of the literature.

Discussion

The literature demonstrates that there is undeniably a relationship between cardiovascular disease, schizophrenia and premature morbidity and mortality[1-5]. Individuals with schizophrenia are losing 10-25 years of their life compared to the general population, most commonly due to CVD complications[1-3].

This relationship is a complex one, and there is no obvious cause and effect for the increased incidence of CVD morbidity and mortality in the schizophrenia population. The literature clearly indicates that the medications we prescribe to treat schizophrenia are a

contributing factor. These anti-psychotic medications have side-effect profiles that directly cause dyslipidemia, metabolic syndrome and obesity[5, 6, 10, 15]. In this sense, a direct line can be drawn between anti-psychotic medications and cardiometabolic risk factors. There are some researchers that disagree with this line of thought[16], but the majority of the available research overwhelmingly agrees that the increase in CVD risk factors associated with the medications is related to the increased CVD morbidity in this population.

Social factors of schizophrenia are also linked to an increase in cardiovascular risk factors. Tertiary symptoms of schizophrenia expressed as a disability in daily function are associated in the literature to cardiovascular risk factors. Low socioeconomic status and chronic schizophrenia are closely tied[1,27], and less affluent individuals are more likely to be physically inactive, have poor diets, eat less fruits and vegetables and have less access to healthy foods[24,28]. Symptoms of schizophrenia also are stigmatized[1], within both the general population and medical community. This can affect access to healthcare and treatment, both which can influence cardiovascular outcomes[22]. The natural progression of schizophrenia itself can present as symptoms of poor hygiene and self-care as well as a lack of motivation[6,7,28], all of which can contribute to an overall poor quality of health.

A new and exciting area of research associated with the progression of schizophrenia is inflammation. While there is much evidence within the literature that there are increased inflammatory markers (biological markers that get released when inflammation is present in the body) associated with schizophrenia[12-14], there currently is no clear tie to cardiovascular disease. Researchers are postulating that there is a link between the inflammatory theory of gut microbes (associated with metabolic syndrome, a CVD risk factor) and schizophrenia but no significant statistical evidence has been found to support this theory[13]. The continued theme throughout the

literature is that more studies need to be done, as there will be significant findings once the research techniques are honed further[12-14]. If this is true, there will be profound implications for our abstract understanding of both the hereditary and genetic causes of schizophrenia and it's connections to CVD.

Conclusions

Premature mortality and morbidity due to cardiovascular disease in schizophrenia is a public health issue that demands further research and resource allocation. Individuals with schizophrenia are often overlooked and fall through the cracks of our medical system due to lack of understanding and stigma[1]. This has caused profound disparities resulting in a mortality gap that needs to be addressed as it will continue to widen for the schizophrenia population.

Funding for new research is currently being focused on biological and hereditary causes of schizophrenia and it's association with CVD, specifically inflammatory causes[12-14]. Statistically significant results from this research would be invaluable, allowing us to specifically target medications and interventions to reduce inflammation and therefore reduce both mental health symptoms and CVD risk factors.

Resource allocation into programs implementing services and interventions for individuals with schizophrenia to reduce CVD risk factors (such as metabolic syndrome, physical inactivity, cigarette smoking) is essential. These services and interventions need to be implemented in an evidence-based, systematic approach to be of value, as the research shows mixed results of interventions[13,19,21,22]. Careful monitoring and continued public health oversight into this issue will allow for a systematic approach to intervention that will ideally begin to reduce the mortality and morbidity disparity for individuals with schizophrenia.

There also would be value in programs or seminars offered to the medical community addressing stigma and misconceptions around schizophrenia. This intervention could improve provider's attitudes towards patients with schizophrenia and catalyze change in engagement and access to healthcare visits for this population. Conversely, seminars or trainings could also be offered within the mental health community on how to integrate physical health interventions into their practice. Continued advocacy by public health organizations like Healthy People 2020[20] to integrate physical and mental health services and encourage active communication between the two communities is also key to ensure that both CVD and schizophrenia are being addressed concurrently.

Premature cardiovascular morbidity and mortality is affecting individuals with schizophrenia. This is a public health issue that concerns the medical community. We have the tools and resources to address and begin to resolve the contributing disparities. With a continued, collaborative effort as medical providers we can close the mortality gap and ensure a healthier and happier quality of life for all of the people that we serve.

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